Linezolid and Serotonergic Drugs – The Risk of Serotonin Syndrome

- Serotonin syndrome is defined as a toxidrome marked by excess serotonin receptor activity or neurotransmission.[1]
    - Classic triad of symptoms: neuromuscular abnormalities, autonomic hyperactivity, and altered mental status[2]
- Linezolid is a weak, reversible inhibitor of monoamine oxidase.
- Linezolid may be a preferred agent in many clinical scenarios given its activity against resistant gram-positives, oral formulation, high bioavailability, and cost. Initiation of linezolid in the setting of concomitant serotonergic drugs may cause clinicians concern.
- However, serotonin toxicity associated with linezolid appears to be rare and unpredictable even in the setting of multiple concomitant serotonergic agents.
    - Between January 2000 and December 2019, there were 11,429 reports of serotonin syndrome documented, 669 (5.9%) of which mention Linezolid as or among suspected causes.[4]
    - However, a review of 32 documented cases from the literature and FDA's post-marketing data showed that 11 of the 32 cases did not meet diagnostic criteria for serotonin syndrome (Hunter and Sternbach's criteria).[5]
    - Another large assessment of Phase III and IV clinical trials by Butterfield and colleagues, evaluated 5,426 patients on linezolid and 5058 patients on comparator drugs with concomitant serotonergic agents. The authors reviewed serotonergic adverse events in both groups. Demographics were similar. Only 13 of 5426 (0.24%) of patients with linezolid and 6 of 5058 (0.12%) in the comparator group met criteria for serotonin toxicity. There were 1 (0.08%), 3 (0.55%), and 5 (1.29%) patients taking linezolid plus one, two, or >2 serotonergic agents, respectively.[6]
    - A VA observational matched cohort study evaluated the risk of serotonin toxicity with linezolid vs. vancomycin. Of 251 matched pairs of patients receiving similar proportions of SSRIs, serotonin toxicity was identified in fewer patients receiving linezolid than vancomycin.[7]
- In most cases, use of linezolid in patients receiving other serotonergic drugs should not cause significant concern. However, linezolid should be used in caution with multiple serotonergic agents due to inherent risk for added toxicity risk.

The table below seeks to guide clinical practitioners on who is at risk for serotonin syndrome by concomitantly prescribed agent(s) by indicating which agents confer minimal risk or would warrant further monitoring when used in combination with Linezolid.

PLEASE NOTE: Monoamine oxidase inhibitors (Selegiline, Rasagiline, Phenelzine, and others) have been excluded from this table due to their mechanism of action and well-documented incidence for causing serotonin syndrome. It is not recommended to combine MAO-Is with any serotonin retaining drug, including Linezolid.

Risk of Serotonin Syndrome between Linezolid and Serotonergic Drugs

Serotonergic Drug	Suggestion
Amitriptyline	Consider monitoring
Amphetamine	Minimal risk
Bupropion	Minimal risk
Buspirone	Consider monitoring
Carbamazepine	Insufficient evidence
Citalopram	Consider monitoring
Cyclobenzaprine	Insufficient evidence
Desvenlafaxine	Consider monitoring

Dextroamphetamine	Minimal risk
Dexmethylphenidate	Minimal risk
Dextromethorphan	Minimal risk
Duloxetine	Consider monitoring
Escitalopram	Consider monitoring
Fentanyl	Consider monitoring
Fluconazole	Minimal risk
Fluoxetine	Consider monitoring
Fluvoxamine	Consider monitoring
Imipramine	Consider monitoring
Lamotrigine	Minimal risk
Lithium	Minimal risk
Meperidine	Consider monitoring
Methadone	Consider monitoring
Methylphenidate	Insufficient evidence
Metoclopramide	Consider monitoring
Mirtazapine	Consider monitoring
Ondansetron	Minimal risk
Paroxetine	Consider monitoring
Ritonavir	Minimal risk
Rizatriptan	Minimal risk
Sertraline	Consider monitoring
Sumatriptan	Minimal risk
Tramadol	Consider monitoring
Trazodone	Consider monitoring
Valproic Acid	Minimal risk
Venlafaxine	Consider monitoring
Vilazodone	Minimal risk

Remember: The incidence of serotonin syndrome is extremely low. A rating of “consider monitoring” is not a contraindication to using Linezolid and only a way to identify patients at risk who will require additional monitoring and counseling.

Remember: Agents with a “minimal risk” rating should not be mistaken as “cannot cause serotonin syndrome”. This list is strictly the level of risk a patient would incur when using [agent] + Linezolid.

How to Interpret:

- Minimal Risk: Evidence in the literature suggests extremely low incidence of concomitant drug interaction with Linezolid. Linezolid + [agent] can be used together for short time periods (<14 days) with reasonable certainty of patient safety.
- Consider Monitoring: Evidence in the literature suggests low incidence of drug-drug interaction with Linezolid, but this risk increases with added serotonergic drug burden. Consider monitoring this patient, especially as agents are added/dose-titrated, for serotonin syndrome.

Drugs (illicit and non-) with serotonergic properties with minimal reports of Linezolid DDI in the current literature: Desvenlafaxine, Desipramine, Clomipramine, Nortriptyline, Oxycodone, Morphine, Buprenorphine, Propoxyphene, Codeine, Hydromorphone, Droperidol, Dolasetron, Granisetron, Ondansetron, Sumatriptan, Oxitriptan, Rasagiline, Methamphetamine, Amphetamine, Tryptophan, Modafinil, Dextromethorphan, Entacapone, Psilocybin, LSD, Ecstasy, Cocaine

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